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Central nervous system control of the laryngeal muscles in humans

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Abstract

Laryngeal muscle control may vary for different functions such as: voice for speech communication, emotional expression during laughter and cry, breathing, swallowing, and cough. This review discusses the control of the human laryngeal muscles for some of these different functions. Sensori-motor aspects of laryngeal control have been studied by eliciting various laryngeal reflexes. The role of audition in learning and monitoring ongoing voice production for speech is well known; while the role of somatosensory feedback is less well understood. Reflexive control systems involving central pattern generators may contribute to swallowing, breathing and cough with greater cortical control during volitional tasks such as voice production for speech. Volitional control is much less well understood for each of these functions and likely involves the integration of cortical and subcortical circuits. The new frontier is the study of the central control of the laryngeal musculature for voice, swallowing and breathing and how volitional and reflexive control systems may interact in humans.

Keywords

Speech; Voice; Swallowing; Respiration; Cough; Laryngospasm

1. Laryngeal muscles

Laryngeal muscle control requirements in humans differ between voice production for speech, swallowing, respiration and cough. For each of the laryngeal functions, different vocal fold movements are required: maximally open during sniff; open during inhalation; less open during exhalation; partially open (paramedian) during voiceless consonants such as /s/; closed in the midline for vocal fold vibration during voice production; elongated for high pitched voicing and singing; tightly closed to offset vibration during glottal stops in speech and cough; and, sphincteric closure of both the vocal and ventricular folds during valsalva and swallowing.

Voice is produced as the vocal folds are held in the midline of the glottis and air flow from the lungs causes increases in the subglottal pressure for opening the vocal folds. As the vocal folds open, the airflow passes between the folds reducing the pressure between them (the Bernoulli effect), and the muscle tension in the folds returns them to the midline for closure, allowing the cyclic process to continue (Titze, 1994). This passive vibration will continue as long as there is a trans-glottal pressure difference; that is a higher subglottal than the supraglottal pressure causing air flow across the folds to induce vibration. Although vocal fold vibration is passive, the speaker has to maintain an adequate respiratory flow during exhalation and use adequate muscle activity to keep the vocal folds in the midline for vibration to occur. Speech

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requires rapid and precise muscle control for voice onsets and offsets within a few milliseconds to make linguistic distinctions between voiced and unvoiced sounds, such as /d/ versus /t/.

The laryngeal muscles are classified as either intrinsic (confined to the larynx) or extrinsic (attaching the larynx to other structures within the head and neck). Vocal fold movements are described as adductor (vocal fold closing) and abductor (opening). Intrinsic laryngeal muscles are usually classified as having either an adductor action (thyroarytenoid (TA), lateral cricoarytenoid (LCA), interarytenoid (IA)) (Fig. 1A) or abductor function (posterior cricoarytenoid (PCA)) (Fig. 1B), while the cricothyroid (CT) muscle can elongate the vocal folds (Fig. 1C and D). The extrinsic laryngeal muscles (the thyrohyoid and the sternothyroid) change the position of the larynx in the neck by raising or lowering the thyroid cartilage, respectively. The thyrohyoid muscle plays an essential role in raising the larynx during swallowing while the sternothyroid muscle may lower voice pitch.

Most of the functions that involve the larynx require both intrinsic and extrinsic muscle control, although very little research has addressed how the effects of the intrinsic and extrinsic muscles may interact to produce laryngeal movement. Honda et al. (1999) have shown that raising and lowering the fundamental frequency of vocal fold vibration can depend upon the interaction between an intrinsic laryngeal muscle, the CT, and an extrinsic muscle, the sternothyroid. The CT muscle increases the angle between the cricoid and thyroid cartilages (Fig. 1D) thus elongating the folds to increase tension and the rate of vibration. The sternothyroid lowers the larynx along the curvature of the spine, reducing the angle between the cricoid and thyroid cartilages, shortening the folds and lowering the frequency of vibration.

The action of each of the laryngeal muscles on vocal fold movement is dependent upon multiple interacting factors. Unopposed CT muscle contraction will lengthen the folds, while unopposed TA muscle contraction will shorten the vocal folds (Fig. 1A). These two opposing muscles are used synergistically throughout the pitch range to alter the frequency of vocal fold vibration by changing vocal fold length and tension (Titze et al., 1989). Furthermore, the CT muscle may play different roles in movement depending upon vocal fold position at the time of contraction; it raises vibratory frequency when the vocal folds are in the midline for voicing (Titze et al., 1989; Kuna et al., 1994), is active for abduction during inspiration and sniff (Kuna et al., 1994; Poletto et al., 2004) and during vocal fold opening for voiceless consonants during speech (Lofqvist et al., 1984).

Most intrinsic laryngeal muscles change vocal fold position by moving the arytenoid cartilages relative to either the cricoid cartilage (the PCA and LCA muscles); the thyroid cartilage (the TA muscle); or the contralateral arytenoid cartilage (the IA muscle). The arytenoid movement resulting from multiple muscle contractions is highly dependent upon the geometry of the cricoarytenoid joint. The LCA and the PCA both insert on the muscular process of the arytenoid cartilage and the direction of movement will depend upon the relative co-contraction of these opposing muscles. With 3D imaging, the geometry of the cricoarytenoid joint was shown to allow a rocking action from lateral and superior for opening the folds (abduction) (Fig. 2), to a medial and inferior direction for closing the folds in the midline (adduction) (Fig. 2) (Selbie et al., 1998) as was originally proposed by Maue and Dickson (1971).

Many laryngeal muscles contain different compartments with a variety of fiber orientations and insertions. The CT muscle contains at least two compartments, the rectus and oblique, which are considered to have different actions (Fig. 1C and D). The rectus closes the angle between the cricoid and thyroid cartilages, tilting the front of the thyroid cartilage downwards thus elongating the folds (Fig. 1D). The action of the oblique portion is controversial. Although originally proposed to slide the thyroid cartilage forward over the cricoid cartilage (Fig. 1D) (Maue and Dickson, 1971; Fink, 1975), this has not been observed in humans and may not be

feasible given the characteristics of the cricothyroid joint and ligament (Reidenbach, 1995; Hong et al., 2001). Other laryngeal muscles with separate compartments that are likely to have different actions are the lateral and medial portions of the PCA (Bryant et al., 1996) (Fig. 1B) and the lateral and medial portions of the TA (Sanders et al., 1998). The muscle fibers in the vestibular fold, which are present in the human but are largely absent in other species, were studied in 32 human larynges (Reidenbach, 1998). Different fiber bundles were described that may play a role in vestibular fold shaping both for speech and sphincteric control. The muscle in the vestibular fold often remains active in the case of recurrent laryngeal nerve injury and may be innervated by the superior laryngeal nerve (Sanders et al., 1993; Reidenbach, 1998). Three separate compartments of the vestibular muscle were hypothesized to produce medial movement, often seen during glottal stops in speech, as well as inferior movement, which may add to sphincteric closure during swallowing.

Although many textbooks propose separate actions for each of the laryngeal muscles (Tucker, 1987; Emlin, 1988), relatively limited quantitative data is available on laryngeal biomechanics. One possible reason is measurement accessibility, which remains a central problem in the human. The usual approach to laryngeal imaging, using either a rigid laryngoscope or a fiberoptic nasoendoscope, provides only a superior perspective that reflects movement in the superior–inferior dimension onto the lateral–medial and anterior–posterior planes. Two investigations using three-dimensional imaging of cadaveric larynges, demonstrated how viewing from a superior perspective has erroneously distorted our understanding of arytenoid and vocal fold movement (Woodson et al., 1997; Selbie et al., 1998). With the availability of high resolution dynamic three-dimensional imaging techniques, less flawed studies of human laryngeal biomechanics can be conducted. Studies of the force vectors of the laryngeal muscles and their compartments should improve understanding of the actions of the laryngeal muscles in humans.

2. Muscle control for different laryngeal functions

The physiological study of the laryngeal muscles in humans is challenging given the difficulties with obtaining accurate electromyographic (EMG) recordings from these relatively inaccessible muscles. Although some studies have used visual placement during surgery (Hong et al., 2001), most investigators use percutaneous insertions of either needle or hooked wire electrodes. Placement is verified using standard gestures that will elicit activation in a target muscle to assure an accurate location of the recording electrode (Hirano and Ohala, 1969). For example, a sniff will elicit increased activity in the PCA while throat clear will activate the TA muscle. Laryngeal EMG requires considerable skill and care and may account for some of the differences in results between studies.

Studies of laryngeal muscle control for respiration, voice and speech, cough and swallowing have progressed relatively independently. Selected results will be reviewed here to illustrate some of the commonalities and differences in the control of various laryngeal functions.

2.1. Differences in laryngeal muscle control

Variation between and within individuals on how the laryngeal muscles are used may be more evident for a learned motor skill such as speech, in comparison with more reflexively controlled laryngeal motor patterns such as cough and sniff. A preliminary cross-correlation study examined the relationship between intrinsic muscle activity and vocal fold movement during syllable repetition, cough or throat clear, and sniff (Poletto et al., 2004). By doing a list-wise correlation between a smoothed EMG recording and the change in the opening angle of the vocal folds over time, the relationship between laryngeal muscle activity and movement was determined. This identified what types of movement occur when a particular muscle becomes active. Only the PCA muscle was correlated only with movement in one direction, vocal fold

opening, in all subjects. The CT muscle was significantly correlated with vocal fold opening only during sniff. The two adductor muscles studied, the TA and LCA, were significantly correlated with vocal fold closing only during cough. During speech, the CT and TA muscles were correlated with both opening and closing. Reciprocal muscle activity only occurred on cough, while speech and sniff involved simultaneous contraction of muscle antagonists. The subjects had relatively consistent patterning of their laryngeal muscles in cough. In speech, developed as a result of motor learning, the subjects used a variety of patterns of opposing muscle activations to achieve the required vocal fold movements.

2.2. Respiration

The laryngeal muscles provide active vocal fold opening to enhance flow intake during inspiration and partial closing to reduce air flow during expiration (Fig. 2). During inspiration, the PCA muscle is phasically active (Brancatisano et al., 1991) and activity of the CT tends to increase (Woodson, 1990) while the TA muscle is more active during expiration (Kuna et al., 1988). Not all of the motor neurons are phasically active with respiration during breathing in awake humans. When the firing patterns of single motor units were examined with reference to the respiratory cycle, both tonic and phasic motor unit firing patterns were found in the TA and CT muscles in 10 normal adults (Chanaud and Ludlow, 1992). The tonically firing units had higher firing frequencies than those with phasic firing during inspiration. A variety of complex motor unit firing patterns were evident within muscles demonstrating that the firing patterns of many laryngeal motor neurons are not tightly coupled to the respiratory rhythm in awake humans.

Changes in respiratory state have fairly reliable effects on the intrinsic laryngeal muscles. With hypocapnia due to hyperventilation, the PCA muscle becomes quiet while the adductor muscles become more active to reduce the glottic aperture (Kuna et al., 1993a, 1993b). During hypercapnia, the adductor muscles become less active (Kuna et al., 1993a, 1993b) and the CT muscle becomes more active (Woodson, 1990). These studies have demonstrated that respiratory reflexes have an active role in controlling the laryngeal muscles in awake humans (Woodson, 1990). During more volitional tasks, however, such as forced vital capacity, a task that requires some training and learning in naïve normal adults, both the adductor and abductor muscles become simultaneously active (Kuna and Vanoye, 1994). The laryngeal muscle activation patterns used for volitional tasks that involve some motor learning are more complex and less consistent across individuals.

2.3. Swallowing

During the pharyngeal phase of swallowing, a rapid sequence of events is responsible for moving the bolus safely from the oropharynx into the esophagus without aspiration into the airway. The larynx and hyoid bone are moved anteriorly and superiorly in the neck by extrinsic muscles to assist with epiglottal inversion to cover the airway, while closing the vocal folds (Kawasaki et al., 2001). The pharyngeal phase of swallowing is considered reflexive, dependent upon a central pattern generator in the medulla as evidenced by the significant disturbance in the pharyngeal phase that occurs with a lateral medullary stroke—Wallenberg syndrome (Aydogdu et al., 2001). Alimentary swallowing usually includes the oral and pharyngeal phases as one continuum. On the other hand, protective swallows can be initiated reflexively in response to the presence of the bolus either in the faucial pillars (Pommerenke, 1927) or in the pyriform sinuses (Pouderoux et al., 1996). Studies of the sequence of muscle activations in humans have demonstrated a series of activations progressing from jaw and perioral to suprahyoid, tongue, laryngeal and pharyngeal muscles during the swallowing pattern (Gay et al., 1994). Normal subjects vary in the particular sequence and timing of these muscle activations (Gay et al., 1994). This variability may depend on how the sensory input is altered by the bolus (Ertekin et al., 1997), differences in normal sensitivity (Pommerenke, 1927), and

head position (Ertekin et al., 2001). Although the pharyngeal phase of swallowing is reflexive and can be elicited by sensory triggers in the oropharynx, it can also be modulated by volitional control. Both automatic reflexive saliva swallows and volitional swallowing activate cortical regions in awake humans (Martin et al., 2001), suggesting that the reflexive and volitional control systems are integrated to adapt to ongoing changes in motor demands during swallowing in humans.

2.4. Cough

The LCA and TA muscles are active for vocal fold adduction during cough (Poletto et al., 2004). This adduction occurs immediately following inspiration to close off the upper airway and raise the subglottal pressure. Next, the PCA muscle is active for vocal fold abduction (Poletto et al., 2004) to provide high levels of air flow for clearing substances from the upper trachea, larynx and hypopharynx. Cough can be triggered by stimulation of the mucosa in the trachea, glottis and supraglottic region. The cough centers in the medulla have been well characterized in animals (Gestreau et al., 1997). The cough reflex involves some of the same regions in the medulla as those involved in respiratory apnea, swallow and the laryngeal adductor reflex, which are all triggered by stimulation of the afferents in the internal branch of the superior laryngeal nerve (iSLN) (Ambalavanar et al., 2004).

Limited information is available on cerebral mechanisms involved in volitional cough and cough suppression in awake humans (Lee et al., 2002; O'Connell, 2002), although human experience demonstrates that volitional cough generation and suppression is possible. In the cat, Kase found electrical stimulation in the suprasylvian gyrus could initiate cough (Kase et al., 1984). This region may be related to the region for laryngeal muscle motor control in the monkey (Simonyan and Jurgens, 2003). On the other hand, stimulation in the anterior cingulate in the cat suppressed cough induced by iSLN stimulation (Kase et al., 1984). The identification of cerebral control centers for cough elicitation and suppression in the human could be important for improved treatment of chronic cough.

2.5. Speech

Individual differences in use of the laryngeal muscles to achieve the same task are particularly evident during speech. Changes in voice intensity depend upon an interaction between increases in subglottal pressure and vocal fold tension (Baker et al., 2001). When both young and older speakers were studied, all were able to increase and decrease voice intensity from their normal comfortable loudness levels. To increase and reduce voice intensity, speakers increased and lowered their subglottal pressure and fundamental frequency demonstrating a simultaneous change in vocal fold tension during the task. To determine how the laryngeal muscles were used to effect these changes, the authors measured percent change in levels of muscle activation from comfortable loudness levels in the TA, CT and LCA muscles. The speakers varied in how they achieved these changes. Some decreased their TA or LCA muscle activity during low intensity voice production and increased these muscles during high intensity production. However, an equal number of other speakers either increased CT muscle activity levels or adductor activity levels during both the low and high intensity voice productions. Notwithstanding the technical difficulties with human laryngeal muscle EMG, the variation in how the task was achieved across speakers was striking. Speakers may have developed different strategies to achieve the same voice outcome, referred to as "motor equivalence".

Speakers change their laryngeal muscle activation to produce changes in fundamental frequency in phrases or sentences for speech intonation (Atkinson, 1976, 1978). For example, a decrease in fundamental frequency at the end of a sentence usually denotes a declarative statement and probably involves some relaxation of the folds as well as reduced air flow. In contrast, a question requires a rapid rise in the fundamental frequency at the end of the phrase.

The CT muscle appears to be used interactively with the TA muscle to change the fundamental frequency but considerable variability occurs from sentence to sentence and from speaker to speaker on how the muscles are activated (Atkinson, 1976). This is most likely because subglottal air pressure and flow also play a role in voice intensity and fundamental frequency.

Few investigators have recorded from the laryngeal muscles while recording tracheal (subglottal) pressures during speech (Finnegan et al., 1999, 2000). The two studies by Finnegan and coworkers found a complex but independent interaction between variation in laryngeal muscle activity and tracheal pressures demonstrating that speakers control the laryngeal muscles independent from subglottal pressure to produce changes in voice intensity and fundamental frequency.

The most difficult aspect of laryngeal muscle control for speech involves the rapid and precise changes in vocal fold abduction and adduction for voice offset and onset, respectively, during consonant production. Here the speaker must vary subglottal pressure and laryngeal muscle activity to change vocal fold opening within a few milliseconds for linguistic contrasts. To produce an /h/, the speaker must open the vocal folds to an adequate degree to offset voice for the listener to perceive a voiceless glottal fricative. When voice offset for the voiceless consonant /h/ was examined across male and female speakers in adults and children, the groups used different durations of voice offset (Koenig, 2000). These differences may depend upon vocal fold size and shape. That is, because adult males have greater vocal fold mass resulting in larger self-oscillation forces, adult males produce less voice offset for an /h/ which listeners still perceive as voiceless sounds in these speakers.

For all other voiceless consonants besides /h/, narrowing or obstruction in the oral tract above the larynx produces either turbulence or stoppage of the air flow, resulting in an increase in the supraglottal pressure. Because transglottal pressure differences must be maintained to continue air flow between the folds for vibration, the rapid supraglottal changes are accompanied by precise changes in vocal fold tension, opening and subglottal pressure to maintain voicing. Recordings of the laryngeal muscles during repetition of syllables such as /si-si-si-si/ have shown that speakers independently control the muscles on the two sides of the larynx from syllable to syllable (Ludlow et al., 1994). This variation indicates that a speaker may make different adjustments in the muscles on the two sides to accommodate for ongoing changes in subglottal and supraglottal pressure and flow (Ludlow et al., 1991). The complexity and rapid dynamic control of the laryngeal musculature used by speakers in everyday life to achieve these volitional but seemingly automatic gestures, demonstrates the remarkable skill that humans develop to produce intelligible speech.

3. Sensori-motor reflexes affecting laryngeal muscle control

Numerous reflexes affect laryngeal muscle control and are contained within the central pattern generators for airway protection during cough and swallow. Laryngospasm may represent an abnormal excitation and/or loss of inhibition of the laryngeal closure reflex (Suzuki and Sasaki, 1977). Most laryngeal reflexes are elicited by stimulation of the laryngeal afferents contained in the iSLN in awake humans, although animal studies suggest that afferents in the recurrent laryngeal nerve may also have a role in laryngeal muscle control (Shiba et al., 1997; Clark and Farber, 1998). These reflexes demonstrate that sensory feedback may contribute to laryngeal muscle control and that central mechanisms may normally control these reflexes during volitional laryngeal tasks such as voice production for speech.

Aviv et al. (1999) developed a non-invasive method for presenting rapid changes in air pressure to the mucosa overlying the arytenoid cartilages in humans and found that persons could reliably perceive air puff stimuli that elicited a vocal fold closure reflex. The laryngeal adductor reflex is a TA muscle response that can also be elicited in humans with a brief electrical stimulus

to the iSLN (Ludlow et al., 1992). This response has been extensively studied in cats (Sasaki and Suzuki, 1976; Suzuki and Sasaki, 1977) and involves afferents terminating in the interstitial subnucleus of the nucleus tractus solitarius, the area postrema, the lateral tegmental field and the nucleus ambiguus (Ambalavanar et al., 2004). The human response to electrical stimulation of the iSLN (Fig. 3) contains an early ipsilateral R1 response (at 17 ms) and a later bilateral R2 (at 65 ms) (Ludlow et al., 1992), similar to the blink reflex in humans (Sanes and Ison, 1983). The R2 component of the laryngeal adductor response and the blink reflex both show conditioning effects (Sanes and Ison, 1983; Ludlow et al., 1995). That is, with repeated stimulation, responses are reduced in both frequency of occurrence and amplitude demonstrating a role of central inhibition modulating R2 responses. Laryngeal adductor responses to mucosal air puff stimuli in humans (Fig. 3) occur after 80 ms and are similar to the R2 response to electrical stimulation of the iSLN (Bhabu et al., 2003). Recently central suppression of the R2 response (both in frequency of occurrence and amplitude) was demonstrated when inter-stimulus intervals between two air puffs were less than a second in normal subjects (Kearney et al., 2005). During speech and swallowing, closure of the vocal folds will provide similar pressures to the mechanoreceptors in the laryngeal mucosa as those produced by airpuff stimuli. Because R2 muscle responses could disrupt speech, central suppression of such responses to mucosal deflection likely plays a significant role in controlling these reflex responses during speech.

The laryngeal adductor response involves afferent fibers contained in the iSLN with the cell bodies in the nodose ganglion terminating in the nucleus tractus solitarius (Sessle, 1973; Mrini and Jean, 1995; Gestreau et al., 1997; Ambalavanar et al., 2004). On the other hand, the afferents involved in cough are located in the tracheal bifurcation and are also thought to have their cell bodies in the nodose ganglion although in the guinea pig these are contained in the jugular ganglion (McAlexander et al., 1999). The dorsal swallowing center in the nucleus tractus solitarius contains central patterning for swallowing with input to the laryngeal motor neurons via the solitari-ambiguus pathway (Jean, 2001). Similar inputs, therefore, are involved in both the swallowing pattern generator and the laryngeal adductor response, and both systems produce adduction of the vocal folds via the laryngeal motoneurons in the nucleus ambiguus.

The central interaction between volitional swallowing and the laryngeal adductor response was studied in awake humans by stimulating the iSLN to elicit the laryngeal adductor response at various time points during the pharyngeal phase of swallowing (Barkmeier et al., 2000). The R1 response was reliably elicited at all times while the R2 response was actively suppressed during swallowing and for up to 3 s after the onset of the pharyngeal phase of swallowing. Therefore, in awake humans not only is the R2 laryngeal adductor response actively suppressed with repeated mucosal stimulation, but it is also suppressed during volitional swallowing. It is not yet known whether active suppression of these reflex responses is due to modulation of the reflex circuits within the medulla or by cortical modulation of the brain stem laryngeal adductor pathway during voice and swallowing. Because the R2 muscle response to electrical stimulation is similar to muscle responses that occur with increased pressure to the mechanoreceptors in the glottis (e.g. air pressure) (Fig. 3), suppression of this response may reduce laryngeal adductor responses to mucosal pressure that occurs during swallowing. In this way the laryngeal adductor response may be less likely to interfere with airway opening for inhalation immediately following the completion of a swallow.

The pharyngoglottal closure reflex, also involves a vocal fold closure reflex in awake humans, and occurs in response to a rapid pulse of water injected towards the posterior pharyngeal wall (Shaker et al., 2003). When the water infusion is increased or is continuous, a full swallow is elicited. Thus, although the laryngeal adductor response is suppressed during swallowing (Barkmeier et al., 2000), another laryngeal closure reflex is contained within the central pattern generator for a reflexive pharyngeal swallow. The glossopharyngeal nerve is the afferent limb

for the pharyngoglottal reflex, although the brain stem control system is still not defined (Shaker et al., 1998). The degree to which the pharyngoglottal reflex can be modified by other functions such as voice production has not yet been addressed.

4. The role of sensory feedback in laryngeal control

The role of sensory feedback from the larynx in volitional control for voice and swallowing has been studied. Although oral afferents were reported to play a role in humans' sense of their ability to initiate a swallow (Pommerenke, 1927), afferents contained in the iSLN were shown to play an essential role in volitional swallowing in humans (Jafari et al., 2003). A comparison of the effects of bilateral bupivacaine anesthesia of the iSLN in contrast with saline injections in the same region, demonstrated that with afferent blockade swallowing became effortful with increased frequency of laryngeal penetration and tracheal aspiration due to incomplete laryngeal closure. On the other hand, the bilateral block did not alter other laryngeal gestures for valsalva and cough. In another study, the effects of lidocaine to the iSLN were minimal on voice (Gould and Tanabe, 1975). This suggests that integrity of the afferents contained in the iSLN is essential for swallowing but not for voice production.

Certainly, the precise and rapid control of the laryngeal muscles during speech suggests that somatosensory feedback was used during development to learn to produce certain vocal fold movements when developing voice control for speech. The role of speech perception in guiding the development of laryngeal control for speech is seen in children who are congenitally deaf because despite extensive training they usually have life long difficulties with voice control. Similarly, adults with acquired hearing loss gradually develop difficulties with controlling voice loudness and pitch.

Larson and coworkers conducted a series of studies demonstrating the dynamic interplay between auditory self-monitoring and pitch control in adults during voice production (Larson et al., 1996, 2000; Burnett et al., 1997). Normal adults produce rapid compensatory changes in their voice pitch in response to changes in auditory feedback; when the frequency of the feedback is shifted downward, subjects increase their voice pitch and vice versa (Burnett et al., 1997). Speakers are not always aware, however, that they are making these corrections. Recently, these compensatory responses were shown to play a role in ongoing speech and singing control (Leydon et al., 2003; Xu et al., 2004). Interestingly, pitch shift responses were greater in persons who speak tonal languages than in English speakers. This suggests the pitch shift response is not a simple laryngeal reflex but part of the dynamic ongoing control of the laryngeal musculature for linguistic communication.

The ongoing use of somatosensory feedback from the larynx in volitional motor patterns for speech, swallowing and respiration has been less well studied. One issue has been which types of receptors play a role in laryngeal feedback. Afferents contained in the iSLN were found to be highly sensitive to mucosal deflection in the cat and rabbit (Davis and Nail, 1987). Many of these were rapidly adapting, firing in response to both stimulus onset and offset. Further, the laryngeal adductor response in the cat can be elicited only by deflection of the mucosal receptors and not by muscle stretch, cricoarytenoid joint or tendon displacement (Andreatta et al., 2002). Considerable controversy has continued over whether there are spindles in the laryngeal muscles. The most recent findings suggest that spindles occur only in the interarytenoid muscle and are sparse or absent in the TA, LCA, CT and PCA muscles (Ibrahim et al., 1980; Brandon et al., 2003; Tellis et al., 2004). No studies to date have demonstrated a physiological effect of muscle stretch in the human larynx.

Two studies have reported on laryngeal responses to a servomotor induced deflection of the thyroid cartilage which will lengthen the CT muscle, shorten the TA with the initial application and then lengthen the TA with withdrawal of force (Fig. 4) (Sapir et al., 2000; Titze et al.,

2002). One study reported an immediate lowering of the fundamental frequency that likely reflects the mechanical effects of vocal fold shortening with servomotor force application (Fig. 4) (Sapir et al., 2000). This was followed by a second voice change that increased the fundamental frequency beginning at around 100 ms (Fig. 4). These authors reported that the second voice change followed a surface EMG response at around 40 ms, which was recorded on the skin overlying the larynx. The EMG response may have included responses from the sternothyroid muscle that is attached to the thyroid cartilage and was lengthened during the initial force application (Fig. 4). The other study recorded from the CT and TA muscles in two subjects (Titze et al., 2002) and found a response at around 40 ms in the CT. It cannot be determined if these muscle responses represented a compensatory pitch shift response to the audible pitch lowering with force application (Burnett and Larson, 2002) or stretch responses in either the sternothyroid or CT muscles. The possibility of a CT muscle stretch response is less likely given the paucity of muscle spindles in that muscle (Ibrahim et al., 1980).

Many authors have hypothesized that stretch reflexes in the laryngeal muscles might provide pro-prioceptive feedback for voice control (Kirchner and Wyke, 1965; Abo-El-Enein and Wyke, 1966; Wyke, 1974). The elicitation of the laryngeal adductor response by air puff stimuli and participants' perceptions of these stimuli to the laryngeal mucosa (Bhabu et al., 2003), demonstrate that mechanoreceptors in the laryngeal mucosa provide dynamic sensory feedback in humans. Current evidence supports a role for mucosal mechanoreceptors in providing feedback to the central nervous system in humans during laryngeal movement.

Auditory masking is the use of white noise, usually presented through earphones, to block out feedback of one's own speech. The effects of auditory masking have been contrasted with the effects of blocking mucosal afferents on voice control of fundamental frequency in single tones and during sentence intonation in normal speakers (Mallard et al., 1978). Auditory feedback was shown to play a greater role in the control of fundamental frequency than afferent feedback in these speakers. On the other hand, afferent information may be important for accurate pitch control in trained singers who can accurately initiate voice on a target pitch before auditory feedback becomes available (Sundberg et al., 1996). The authors proposed that intonation patterns "appeared to be programmed into the speech production system at a "high level" independent of peripheral monitoring" (Mallard et al., 1978). The pitch shift studies by Larson and coworkers (Burnett et al., 1998; Larson et al., 2000) suggest that even when intonation patterns are pre-programmed, a perturbation in auditory feedback can have an immediate effect on pitch control presumably via changes in laryngeal muscle activity. It remains to be seen to what degree perturbations affecting mucosal sensation can alter laryngeal control in humans.

5. Central nervous system control of volitional laryngeal control

Each of the functions involving laryngeal muscle control includes reflexive central pattern generators either in the medulla for cough, swallow, and respiration, or in the periaqueductal grey and nucleus retroambiguus (also referred to as the retroambiguus) for voice production (Zhang et al., 1995). Although these patterns are reflexive and automatic, they must interact with volitional control at higher levels of the central nervous system. The precise interactions between cortical and subcortical control systems and reflexive pattern generators appear to be essential for normal laryngeal function. However, relatively little is known about such interactions.

The animal vocalization system that has been extensively studied by Jürgens and coworkers, includes the anterior cingulate cortex, the periaqueductal grey, nucleus retroambiguus and nucleus ambiguus (Jürgens and Ploog, 1976; Jürgens, 2002). In humans, this system may be involved in emotional expression such as laughter and cry but appears to be of less importance for volitional expression such as voice and speech, which may depend more on cortical control.

Clinical evidence of this dissociation can be seen in spasmodic dysphonia, a laryngeal dystonia, where patients can cry, laugh and shout normally but have abnormalities during speech communication (Izdebski et al., 1984; Brin et al., 1998). Involuntary muscle spasms in spasmodic dysphonia only interfere with voice production for speech (Bloch et al., 1985; Nash and Ludlow, 1996). Perhaps emotional expression uses the older vocalization system found in other species (cingulate cortex, periaqueductal grey, retroambiguus and ambiguus). Speech expression, in contrast, may depend upon relatively direct control of the laryngeal motoneurons by the laryngeal motor cortex at the inferolateral end of the primary motor cortex adjacent to the sylvian fissure (Simonyan and Jurgens, 2003).

Kuypers compared the corticobulbar pathways in the human (Kuypers, 1958b) with those in the monkey (Kuypers, 1958a) and found sparse labeling in the nucleus ambiguus after cortical injection of a tracer in a patient suggesting that there are some direct corticobulbar projections from the motor cortex to the laryngeal motor neurons in the nucleus ambiguus in the human. He found no evidence of a similar direct corticobulbar projection in the monkey and chimpanzee (Kuypers, 1958a), which was further confirmed by a recent study in Rhesus monkeys (Simonyan and Jurgens, 2003). While frontal cortical stimulation can induce rapid neuronal responses in the dorsal swallowing area in the nucleus tractus solitarius in the medulla in sheep (Car, 1973), this author reported that responses in the nucleus ambiguus were delayed suggesting an oligosynaptic response from the cortex to the motor neurons in the nucleus ambiguus. Similar findings have also been reported in the cat (Bassal et al., 1981). Simonyan and Jurgens (2003) used electrical stimulation to identify the laryngeal motor cortex producing bilateral vocal fold closure in Rhesus monkeys and injected an anterograde tracer into the effective site to label subcortical projections. Dense projections with ipsilateral predominance were found in the putamen and thalamus (in the ventral nuclei) with heavy bilateral projections to the brain stem nuclei in the nucleus tractus solitarius. No efferent projections were found in the red nucleus or the periaqueductal grey, or the nucleus ambiguus or retroambiguus in the medulla. Using a retrograde tracer, these authors also found dense projections into the laryngeal motor cortex from the ventrolateral thalamus in the Rhesus monkey (Simonyan and Jurgens, 2005), demonstrating dense reciprocal connections between the basal ganglia and the laryngeal motor cortex.

These results support the conclusion that many of the laryngeal muscle functions for swallowing, cough, respiration and vocalization are controlled by subcortical regions in non-human primates and that direct corticobulbar projections to the nucleus ambiguus may be exclusively human (Simonyan and Jurgens, 2003). Although replication of Kuypers' human results is unlikely, the 12 ms latencies of laryngeal muscle responses to transcranial magnetic cortical stimulation support the possibility of relatively direct projections from the cortex, via a corticobulbar pathway, to the recurrent laryngeal nerve innervating the intrinsic laryngeal muscles (Cracco et al., 1990; Maccabee et al., 1991; Ludlow and Lou, 1996).

Although anatomical connections provide information on regions of connectivity, only functional neuroimaging can provide information on active systems for laryngeal muscle control during respiration, swallowing and voice production in humans. Because changes in blood flow indirectly reflect changes in neuronal firing in the same regions, blood flow changes can be used to examine corresponding changes in brain activity while participants perform volitional tasks. In this way, the functional brain network involved in generating volitional control of swallowing, respiration and voice can be determined. Neuroimaging studies are ongoing and suggest differential involvement of cortical systems for volitional control of the laryngeal musculature for these various functions.

5.1. Neuroimaging studies of respiratory control

Colebatch et al. (1991) first studied cerebral activation during volitional inspiration in six normal subjects using positron emission tomography (PET). They found bilateral activity in the primary motor cortex region thought to control the diaphragm (M1), (Fig. 5A). In addition, activity was also seen in the right pre-motor cortex (PM), the supplementary motor area (SMA) and the cerebellum (CBL) (Fig. 5A). In a subsequent PET study, changes in regional blood flow were contrasted between two tasks: volitional control of inspiration and expiration (Ramsay et al., 1993). Concurrent physiological measures were made to confirm that the five subjects could emphasize inspiration with passive expiration and emphasize expiration with passive inspiration. Both the inspiration and expiration tasks involved increased activity in a high region of the primary motor strip (M1) representing the diaphragmatic, thoracic and abdominal muscles, the SMA thought to be involved in pre-programmed motor movements (Goldberg, 1985) and the right PM area. The major difference between cerebral activation for inspiration and expiration, however, was the greater activation during expiration in the lower part of the primary sensorimotor cortex, the region responsible for laryngeal muscle control (LX) (Fig. 5A). The greater activation in the LX cortex during expiration was surprising given that the laryngeal muscles are more active during inspiration than during expiration during quiet breathing. The authors suggested that the greater activity during expiration in LX might relate to the required volitional control of expiration during vocalization (Ramsay et al., 1993). It is unclear why expiration without vocalization should show activation in the LX and may relate to the limited resolution of the PET technique in 1993.

Functional magnetic resonance imaging (fMRI) can be used to measure blood oxygenation level dependent (BOLD) changes within a shorter time period associated with task performance. In one study the authors contrasted passive ventilation and volitional breathing, as well as inspiration and expiration (Evans et al., 1999). They found activation during inspiration in the same high primary motor area (M1), likely responsible for the diaphragm and chest wall musculature, with left lateralized brain activation for expiration in the inferolateral sensory area and auditory cortex. No activation was seen, however, in LX during either inspiration or expiration. When fMRI was used during other respiratory tasks, no clear activation was found in LX (Evans et al., 1999; McKay et al., 2003) in contrast with the previous results seen with PET (Ramsay et al., 1993). This leaves open the question of whether laryngeal muscle control during volitional breathing tasks in humans is controlled via the cortex or by modulation of other respiratory control centers such as in the medulla.

5.2. Neuroimaging studies of vocalization

Both simple non-linguistic vocalization and voice control for speech articulation involve prolonged expiration. Using PET, one study measured brain activity levels during speech production of a repeated phrase during prolonged expiration and subtracted activity when the same subjects were mouthing the same speech phrase during tidal breathing without voice. The purpose was to identify those regions of brain activity used for voice control for speech along with prolonged expiration (Murphy et al., 1997). A complex pattern of brain activation included: high primary motor activity probably for diaphragm and chest wall control (labeled “mc”); auditory region in the superior temporal lobe activation (tc); and a region labeled “smc2” which the authors denoted as activated for voice and breathing (Fig. 5B). This area was closer to the primary motor region for the lips and jaw for movements for speech articulation and did not involve the laryngeal motor cortex closer to the sylvian fissure (Simonyan and Jurgens, 2003). In addition, there was a symmetric pattern of activation in the two hemispheres and no activation in Broca’s area (Murphy et al., 1997). The use of subtraction methods to identify behavioral components in tasks, however, makes assumptions about additivity that have been widely questioned (Sidtis et al., 1999).

An important study attempted to study vocalization (with expiration) using event related fMRI to measure the hemodynamic response in the BOLD signal after speaking (Huang et al., 2002). By delayed sampling of the hemodynamic response after speech, movement artifacts induced by speaking are avoided (Birn et al., 1999). The authors examined subjects during two conditions, producing overt speech (naming a letter or an animal), and covert speech (silently naming a letter or an animal). Such a contrast keeps the language formulation functions the same in both tasks and the only difference that remains between the two conditions is motor speech production. This contrast allowed the identification of those brain areas that are activated for speech motor control. Huang et al. (2002) measured changes in the BOLD signal over time in three regions in the both hemispheres: the primary motor regions for the mouth, lips and tongue (smc), Broca's area (BA), and the most rostral end of the primary motor cortex which they referred to as the "inferior vocalization region" (the same as LX). The last region most likely included the laryngeal motor cortex (Fig. 5B). When comparing the silent and overt tasks on the two sides, the percent change in the BOLD signal peaked at 6 s equally in the left and right hemispheres in both the mouth, lip and tongue regions as well as in the inferior vocalization region. Activation in Broca's area, however, was greater on the left side for both silent and overt speech during animal naming in contrast with letter naming. The results seem to differentiate speech formulation from the motor aspects of speech production; greater activation occurred in the primary motor cortex for the jaw, lips and tongue (smc) and the vocalization area (LX) bilaterally during overt speech.

The same dissociation between the motor aspects of speech and speech formulation was seen using transcranial magnetic stimulation (Stewart et al., 2001). When magnetic stimulation was over the primary motor region for the lip and jaw muscles on either the right or left sides, speech was disrupted (most likely in "smc"). However, when an anterior site on the left was stimulated without activation of the lip musculature (most likely Broca's area), speech was disrupted, but not with stimulation on the right. Thus, a similar differentiation between a premotor control region for speech articulation (BA) independent from the bilateral motor cortex for the lip, jaw and laryngeal musculature has been suggested using different technologies (Stewart et al., 2001; Huang et al., 2002).

5.3. Neuroimaging studies of swallowing

Volitional swallowing has been studied extensively using functional neural imaging in humans. Multiple regions have been shown to be active including the: primary motor cortex, supplementary motor area (SMA), anterior cingulate cortex (ACC) and right insula (In) (Kern et al., 2001a, 2001b; Martin et al., 2001). The areas of activation for swallowing are more extensive (Fig. 5C), than those active for volitional breathing control (Ramsay et al., 1993; Evans et al., 1999; McKay et al., 2003), or for vocalization with prolonged expiration during speech (Murphy et al., 1997; Huang et al., 2002). This may be because several functions are involved, such as the taste sensation from the bolus, jaw and tongue movement associated with moving the bolus to the oropharynx, and eliciting the reflexive pharyngeal swallow. Water tasting for example, has been shown to produce large regions of bilateral cortical activation, greater in extent and amplitude than cortical activation for a volitional swallow (Zald and Pardo, 2000). Others have shown that tongue movements may also contribute to the brain activation patterns seen during swallowing (Kern et al., 2001a, 2001b). Tongue movement alone can activate a larger region of the cortex and additional regions in the anterior cingulate cortex (ACC), the SMA, precentral and postcentral cortex, premotor, putamen and thalamus besides those regions active for swallowing (Martin et al., 2004). Therefore, cortical control for volitional swallowing may involve voluntary tongue control in addition to taste. On the other hand, cerebral activation for volitional swallowing has not involved the laryngeal motor area at the low end of the primary motor region (Mosier et al., 1999; Kern et al., 2001a, 2001b). In fact, a tongue movement task activated the oral facial primary motor region, close to LX

whereas swallowing did not (Martin et al., 2004). This would suggest that the laryngeal closure component of swallowing is controlled by the central pattern generator in the medulla and not by the cortical activation during volitional swallowing. This most likely also pertains to reflexive or automatic swallowing where cortical activation tends to be less than for volitional swallowing (Kern et al., 2001a, 2001b; Martin et al., 2001). A study of functional activation in the medulla substantiated this; activation was found in the region of the nucleus ambiguus in three individuals during a dry swallow (Komisaruk et al., 2002).

6. Conclusions and future research directions

In summary, cortical control of the laryngeal musculature seems to vary dependent upon the task. Cortical control seems to involve the laryngeal motor cortex more often for voice production during speech than during volitional changes in respiration, with no involvement during volitional swallowing. Perhaps one of the reasons that patterns of laryngeal muscle control vary by task is that the patterning is controlled by different levels within the central nervous system. For example, activation patterns of the laryngeal muscles for speech may involve the left premotor cortex, while the bilateral laryngeal motor cortices may only be active for volitional control of prolonged expiration. On the other hand, laryngeal muscle control during the reflexive pharyngeal phase of swallowing may reside in the medulla swallowing centers. Further studies are needed using event related MRI to study brain activation with greater spatial resolution in response to discrete laryngeal movements for different tasks such as swallow, cough, simple vocalization, prolonged exhalation, syllable production and singing.

As this review has demonstrated, knowledge of laryngeal muscle control is severely limited. Certainly many different life support systems invoke laryngeal movement (respiration and swallowing). Some laryngeal reflexes, when abnormally excited, such as laryngospasm, can be life threatening. In addition, laryngeal motor control for speech is learned over many years in childhood and is impressive in the dynamic precision of the motor control abilities we all develop for speech communication.

Considerable knowledge has been developed about brain stem pathways involved in respiration, cough, and swallowing in animals. New insights are gained about volitional control in awake humans for respiration, speech and swallowing. Very little, however, is known about the various subcortical regions involved in laryngeal motor control in humans. The recent tracing studies in monkey (Simonyan and Jurgens, 2003, 2005) have demonstrated dense reciprocal connections between the laryngeal motor cortex and the putamen and thalamus, yet subcortical control systems and their modulation of cortical and the brain stem centers are virtually unexplored. Significant voice and swallowing deficits seen in Parkinson disease suggest that other regions besides the cortex and medulla are critical to normal laryngeal control for speech and swallowing (Logemann et al., 1977; Robbins et al., 1986). Improved knowledge of the basal ganglia control of the laryngeal musculature might allow for exploration of various neurotransmitter systems to improve laryngeal function in cough, swallow, voice, speech and respiration.

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Fig. 1.

A schematic drawing showing the laryngeal muscles and their attachments on the thyroid, arytenoid and/or the cricoid cartilages. (A) A superior view shows the thyroarytenoid muscle (TA), the lateral cricoarytenoid muscle (LCA) and the interarytenoid muscles (IA). The arrows show the effects of muscle contraction on arytenoid movement. (B) A posterior view shows the lateral (l) and medial (m) compartments of the posterior cricoarytenoid muscle (PCA) and the interarytenoid muscle (IA). (C) A frontal view shows the rectus (r) and oblique (o) compartments of the cricothyroid muscle (CT). (D) A lateral view of changes in position of the thyroid cartilage thought to occur as a result of contraction of the rectus (r) compartment of the CT muscle (a-r) and as a result of the oblique (o) compartment of the CT muscle (b-o). Lengthening of the thyroarytenoid muscle (TA) is shown with contraction of either the rectus or oblique compartments of the CT.

Fig. 2.

A schematic diagram illustrates the motions of the arytenoid cartilage during abduction on the left, and adduction on the right. The numbers illustrate the starting position of the arytenoids cartilage (1), the intermediate position (2) and the final position on the completion of either motion (3). Note that during abduction the tip of the arytenoid, the vocal process, moves from a medial inferior position (1) to a superior lateral position lengthening and elevating the vocal fold (3), while during adduction, the vocal process moves from a superior lateral position (1) to an inferior medial position (3).

Fig. 3.

A thyroarytenoid muscle response is shown in the second tracing from the top following an air pressure puff to the laryngeal mucosa. The air pressure change is shown in the uppermost tracing. The bottom tracing shows the thyroarytenoid muscle response to an electrical stimulation to the internal branch of the superior laryngeal nerve (SLN). Responses to SLN electrical stimulation are labeled as R1 (beginning at approximately 17 ms) and R2 (beginning at approximately 65 ms). The time calibration bar for 100 ms refers to all three tracings.

Fig. 4.

A schematic illustration shows the mechanical effects of a servomotor application of force to the thyroid cartilage. The left top diagram shows the position of the thyroarytenoid muscle (TA), the cricothyroid muscle (CT), and the sternothyroid muscle (ST) at rest. The middle diagram illustrates the change in position as force is applied to the thyroid cartilage (horizontal arrow) pushing it posteriorly and lengthening the CT and the ST muscles. The right top diagram illustrates the change in position of the thyroid cartilage as force is released returning it to the initial position and lengthening the TA muscle. The middle line shows the timing of change in the servomotor force relative to the changes in the fundamental frequency of the voice (bottom tracing). Immediately following force application there is an initial lowering of the fundamental frequency with a later raising (at around 100 ms) and lowering of the fundamental frequency. After a release of force there is a raising of the fundamental frequency followed by a later lowering.

Fig. 5.

A schematic diagram summarizing the results of functional brain imaging studies during volitional breathing (A), during voicing for speech (B), and during volitional swallowing (C). The studies are described in the text. Abbreviations are supplementary motor area (SMA), anterior cingulate cortex (ACC), premotor cortex (PM), motor cortex area for the diaphragm (M1), the laryngeal motor cortex (LX), the cerebellum (CBL), the motor cortex for the diaphragm and chest wall (mc), the motor area active for jaw lips and tongue (smc), the superior temporal lobe area active audition (tc), Broca's area (BA), medulla (M), a large area for taste and tongue movement from the precentral to postcentral gyrus (M1-S1), the insula (In), and the posterior parietal area (PA).